Remarks

Applicants respectfully request that the Examiner reconsider and withdraw the outstanding rejections as they may apply to the amended and newly presented claims.

I. Status of the Claims

Claims 4, 5, 18, 19, 25, 26, 110, and 111 have been cancelled with this amendment. Claims 161-174 have been added. Claims 1-3, 6-17, 20-24, 27-37, 73-77, 79-82, 106-109, 112, 140, and 143-174 are active in the present application.

II. Support for the Amendment

Support for the amendment of claims 1, 3, 15, 17, 22, 24, 106, 107, 109, and 158 is found in the specification, for example, at page 13, line 12 through 20, line 3. Support for new claims 161-174 is found in the specification, for example, at page 58, line 5, and Example 4. Support for new claim 174 is found in the specification at, for example, page 9, lines1-18; page 20, line 13; page 32, lines16-21; and Examples 4-6.

No new matter has been added by this amendment.

III. The Rejection Of Claims 1-29, 79, 140, 154 and 158 Over Israel Must Be Withdrawn

At page 2 of the Office Action of August 1, 2001 (Paper 21), the Examiner maintained the rejection of claims 1-29, 79, 140, 154, and 158 under 35 U.S.C. § 102(b), as allegedly anticipated by Israel, U.S. Patent Number 5,318,898 ("Israel"), or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Israel. Applicants respectfully traverse these rejections.

Claims 1, 15, 22, and 158 are independent claims drawn to methods of cultivating mammalian cells in suspension *in vitro*. Claims 1 and 22 recite methods of cultivating a mammalian cell in suspension *in vitro*, using a medium that is serum-free and chemically defined. Claim 15 recites a method of cultivating a mammalian cell in suspension *in vitro*, using a medium that is chemically defined. Claim 158 recites a method of cultivating a mammalian cell in suspension *in vitro*, using a serum-free, non-animal derived cell culture medium. Each of the independent claims has been amended to exclude dextran sulfate from the medium used in the method. Since Israel is alleged to disclose the use of dextran sulfate but does not disclose or suggest the desirability of using any other polyanionic or polycationic compound, Applicants respectfully submit that this rejection does not apply to the claims as currently presented and respectfully request withdrawal of this rejection.

IV. The Rejection Of Claims 30-37 Over Israel and Ramos Must Be Withdrawn

At page 3 of the Office Action of August 1, 2001 (Paper 21), the Examiner maintained the rejection of claims 30-37, under 35 U.S.C. § 103(a), as allegedly obvious over Israel in view of Ramos *et al.*, WO 92/05246 ("Ramos"). Applicants respectfully traverse this rejection. Claims 30-37 depend—directly or indirectly—from claims 1, 15 or 22 and are drawn to the culture of epithelial cells. As discussed above, claims 1, 15 and 22 have been amended to exclude the use of dextran sulfate. However, neither Israel nor Ramos discloses or suggests the use of any polyanionic or polycationic compounds other than dextran sulfate. Moreover, Ramos does not disclose the use of a chemically defined medium containing dextran sulfate or dextran. Instead, the medium of Ramos contains yeastolate, a hydrolyzed yeast product (see Ramos,

Abstract at line 2; page 4, lines 7-10; and page 8, lines 30-31). The presence of yeastolate, by definition, renders the medium undefined.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). Specifically, there must be a reason, suggestion, or motivation in the cited art that would motivate one of ordinary skill to combine the references, and that would also suggest a reasonable likelihood of success in making or using the invention as claimed as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Applicants submit that neither reference discloses the use of polyanionic or polycationic compounds other than dextran sulfate or dextran, and Ramos does not disclose the use of a chemically defined medium. Hence, the combination of these references does not teach all the limitations of the claims as currently presented. Moreover, one of ordinary skill in the art would not have been motivated to combine the disclosures of these references. Applicants, therefore, respectfully submit that the Examiner has failed to establish a *prima facie* case for the obviousness of the presently claimed invention and respectfully request reconsideration and withdrawal of this rejection as it may be applied to the present claims.

V. The Rejection Of Claims 73-77 and 79-82 Over Israel, Ramos and Inlow Must Be Withdrawn

At page 4 of the Office Action of August 1, 2001 (Paper 21), the Examiner maintained the rejection of claims 73-77 and 79-82, under 35 U.S.C. § 103(a), as allegedly obvious over Israel in view of Ramos and Inlow, U.S. Patent Number 5,024,947 ("Inlow"). Applicants respectfully traverse this rejection.

Claims 73-77 are drawn to methods of producing a virus and claims 79-82 are drawn to methods of producing a polypeptide. Both methods use the step of cultivating a cell according to any one of claims 1, 15, or 22 and, thus, are drawn to the cultivation of *mammalian cells* in suspension *in vitro*. Inlow only discloses the cultivation of *insect cells* using a serum free medium, but has apparently been cited by the Examiner for the proposition that cultivating viruses and producing proteins in serum free media was known in the art. Applicants respectfully disagree.

The present invention is drawn to methods for producing viruses and polypeptide using techniques that involve culturing *mammalian cells*. The Examiner has not identified any disclosure or suggestion in the cited art that would have motivated one of ordinary skill in the art to combine methods of culturing mammalian cells as disclosed by Israel and Ramos with methods of culturing insect cells as disclosed by Inlow. The disclosure contained in Inlow is limited solely to the production of insect viruses in insect cells; there is no disclosure, suggestion or contemplation in Inlow that such methods should or even *could* be applied successfully to the production of viruses in mammalian cells. Absent such suggestion and motivation, the cited references may not be properly combined to render the claimed invention obvious. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988).

Moreover, one of ordinary skill in the art of cell culture would have had no reasonable expectation of success in combining methods of insect cell culture with those of mammalian cell culture. It is well known in the art of cell culture that different cell types have different nutritional and microenvironmental requirements, and therefore require different media formulations. This knowledge is reflected in Ramos where the authors discuss the difficulties of developing serum free media, stating that "[u]nfortunately, the complexity of serum and the differing growth requirements of different types of cells has made it difficult to provide such media." Ramos at page 1, lines 23-26. Thus, contrary to the Examiner's assertion at page 5 of the Office Action, and as explicitly recognized in the very art cited by the Examiner, one of skill in the art would not have reasonably expected successful results cultivating cells from different origins in the same medium. Absent a reasonable expectation of success in combining their disclosures, the cited references may not be combined in the attempt to establish a *prima facie* case of obviousness. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

Applicants submit that the Examiner is improperly combining the references by failing to consider the teachings of each of the references as a whole. MPEP 2141.02 reads in pertinent part:

> A prior art reference must be considered in its entirety, i.e. as a <u>whole</u>, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied* 469 U.S. 851 (1984).

MPEP § 2141.02 (*emphasis in original*). The individual references cited by the Examiner clearly teach away from the combination of their disclosures, and indicate that those skilled in the art would have recognized that methods applicable to one cell type are not *a priori* applicable to

another cell type. Hence, Applicants respectfully submit that the present rejection is improper and request its withdrawal.

VI. The Rejection Of Claims 106 and 143-149, 155 and 157-160 Over Keen Must Be Withdrawn

At page 5 of the Office Action of August 1, 2001 (Paper 21), the Examiner maintained the rejection of claims 106, 143-149, 155 and 157-160, under 35 U.S.C. § 102(b), as allegedly anticipated by Keen, U.S. Patent Number 5,316,938 ("Keen"), or, in the alternative, under 35 U.S.C. § 103(a), as allegedly obvious over Keen. Applicants respectfully traverse these rejections.

A. Anticipation under 35 U.S.C. § 102(b)

A reference anticipates a claim "only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)

Claim 106 as currently presented—and thus dependent claims 143-149, and 155—requires a polyanionic or polycationic compound that is not dextran sulfate. Claim 158—and thus dependent claims 159 and 160—likewise requires a polyanionic or polycationic compound that is not dextran sulfate. Keen does not disclose the use of any polyanionic or polycationic compound. Hence, this rejection is not applicable to claims 106 as currently presented and should be withdrawn.

Claim 157 is directed to a method for replacing protein in a mammalian cell culture medium, the method comprising replacing insulin with a Zn^{2+} salt. Keen does not anticipate the present claim because Keen fails to teach or suggest replacing insulin with a Zn^{2+} salt. This can

be seen by looking at the medium formulations explicitly disclosed by Keen. In Table 1, the medium contains neither Zn^{2+} nor insulin. In the medium WCM4 (column 7) and WCM5 (column 8), Keen includes *both* zinc *and* insulin. There is absolutely no suggestion that zinc can be substituted for insulin. Zinc is described as a non-ferrous metal that may optionally be added to the medium (column 3, lines 46-52) and insulin is described as a growth regulator that may optionally be added to the medium (column 5, lines 35-51). Keen draws no connection between them. Since Keen fails to explicitly or implicitly teach the substitution of zinc for insulin, Keen does not anticipate the claimed invention and Applicants respectfully request withdrawal of this rejection.

B. Obviousness under 35 U.S.C. § 103(a)

As noted above, the burden of establishing a *prima facie* case of obviousness can only be satisfied only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). Specifically, there must be a reason, suggestion, or motivation in the cited art that would motivate one of ordinary skill to combine the references, and that would also suggest a reasonable likelihood of success in making or using the invention as claimed as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for the obviousness of the presently claimed invention and respectfully request reconsideration and withdrawal of this rejection as it may be applied to the present claims.

With regard to claims 106 and 158 and claims dependent thereon, there is no disclosure or suggestion in Keen regarding the use of polyanionic or polycationic compounds. This element of the claimed invention is not present in the cited reference, and the Examiner has not identified any other source that would provide such information. Accordingly, a *prima facie* case of obviousness of the invention of claims 106 and 158 has not been established and Applicants respectfully request reconsideration and withdrawal of this rejection as it may be applied to these claims as currently presented.

With regard to the invention of claim 157, there is no disclosure or suggestion in Keen regarding the substitution of zinc for insulin. This element of the claimed invention is not present in the cited reference, and the Examiner has not identified any other source that would provide such information. Accordingly, a *prima facie* case of obviousness of the invention of claim 157, has not been established and Applicants respectfully request reconsideration and withdrawal of this rejection.

VII. The Rejection Of Claims 150-153 Over Keen Must Be Withdrawn

At page 6 of the Office Action of August 1, 2001 (Paper 21), the Examiner maintained the rejection of claims 150-153, under 35 U.S.C. § 103(a), as allegedly obvious over Keen. Applicants respectfully traverse this rejection.

Claims 150-153 ultimately depend from claim 106 and are drawn to the use of certain concentrations of the medium formulation and certain concentrations of specific components. Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for the obviousness of the presently claimed invention. Since the present claims depend from

claim 106, the inclusion of polyanionic or polycationic compounds in the compositions is one element of these claims. In contrast, and as discussed in detail above, the inclusion of polyanionic or polycationic compounds is not disclosed, suggested or otherwise contemplated in Keen, and the Examiner has not identified any other source that would provide such information. Accordingly, a *prima facie* case of obviousness of the invention of claims 150-153 has not been established and Applicants respectfully request reconsideration and withdrawal of this rejection as it may be applied to these claims as currently presented.

VIII. The Rejection Of Claims 106-112, 143-153, and 156 -160 Over Keen, Israel and Inlow Must be Withdrawn

At page 7 of the Office Action of August 1, 2001 (Paper 21), the Examiner maintained the rejection of claims 106-112, 143-153, and 156-160, under 35 U.S.C. § 103(a), as allegedly obvious over Keen in view of Israel and Inlow. Applicants respectfully traverse this rejection as it may be applied to the claims currently under consideration, specifically to claims 106-109, 112, 143-153, and 156-160.

Claims 107, 108, 109, 112, 143-153, 156 depend—directly or indirectly—from claim 106. Claims 159 and 160 depend from claim 158. As noted above, claims 106 and 158 include the use of polyanionic or polycationic compounds excluding dextran sulfate. This limitation is not present in either the Keen or the Israel reference and the Inlow reference is not properly combined with these references. Accordingly, a *prima facie* case for the obviousness of the invention of these claims—106-109, 112, 143-153, 156, and 158-160—has not been established and Applicants respectfully request reconsideration and withdrawal of this rejection as it may be applied to the amended claims.

Keen does not disclose or suggest the addition of any of the compounds recited in the above-referenced claims to a culture medium. Israel discloses the use of dextran sulfate in a culture medium for mammalian cells, but only demonstrates its use in a single type of cell—CHO cells—and does not suggest the use of any other polyanionic or polycationic compound. Inlow discloses the culturing of insect cells in a serum free medium but, for reasons amply discussed above, cannot be properly combined with references relating to mammalian cell culture. Thus, one of skill in the art would not have been motivated to have combined the disclosures of the cited references, and would have had no reasonable expectation of success in making this combination in the attempt to make and use the presently claimed invention. Hence, a *prima facie* case for the obviousness has not been established and Applicants respectfully request reconsideration and withdrawal of this rejection as it may be applied to the claims as currently presented.

Claim 157 is directed to a method for replacing protein in a mammalian cell culture medium, the method comprising replacing insulin with a Zn^{2+} salt. As discussed above, Keen neither anticipates nor renders obvious the claimed method because Keen does not suggest substituting zinc for insulin. Similarly, the replacement of insulin with zinc is not disclosed in Israel or Inlow, which therefore cannot remedy the deficiencies of Keen. Applicants therefore respectfully submit that a *prima facie* case for the obviousness has not been established and Applicants respectfully request reconsideration and withdrawal of this rejection.

IX. New Claims 161-174 Are Patentable Over The Art Of Record

New claims 161-174 are drawn to methods of culturing 293 cells in suspension culture and none of the cited references discloses or suggests such methods. Accordingly, Applicants

respectfully submit that these claims are patentable and respectfully request early notification of their allowance.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the presently outstanding rejections. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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Version with markings to show changes made

1. (Twice Amended) A method of cultivating a mammalian cell in suspension *in vitro*, comprising:

(a) obtaining a mammalian cell to be cultivated in suspension; and

(b) contacting said cell with a serum-free, chemically defined cell culture medium comprising at least one polyanionic or polycationic compound, wherein said medium supports the cultivation of said cell in suspension, with the proviso that the medium does not contain dextran sulfate.

3. (Amended) The method of claim 2, wherein said polysulfonated or polysulfated compound is selected from the group consisting of [dextran sulfate,] heparin, heparan sulfate, chondroitin sulfate, dermatan sulfate, pentosan sulfate and a proteoglycan.

15. (Twice Amended) A method of cultivating a mammalian cell in suspension *in vitro*, comprising:

(a) obtaining a mammalian cell to be cultivated in suspension; and

(b) contacting said cell with a chemically defined cell culture medium comprising the ingredients ethanolamine, D-glucose, N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid] (HEPES), insulin, linoleic acid, lipoic acid, phenol red, PLURONIC F68, putrescine, sodium pyruvate, transferrin, L-alanine, L-arginine, L-asparagine, L-aspartic acid, L-cysteine, L-glutamic acid, L-glutamine, glycine, L-histidine, L-isoleucine, L-leucine, L-lysine, L-

methionine, L-phenylalanine, L-proline, L-serine, L-threonine, L-tryptophan, L-tyrosine, L-valine, biotin, choline chloride, D-Ca^{++}-pantothenate, folic acid, *i*-inositol, niacinamide, pyridoxine, riboflavin, thiamine, vitamin B_{12}, at least one polyanionic or polycationic compound, one or more calcium salts, KCl, one or more iron salts, one or more magnesium salts, one or more manganese salts, NaCl, $NaHCO_3$, Na_2HPO_4, one or more selenium salts, one or more vanadium salts and one or more zinc salts,

wherein each ingredient is present in an amount which supports the cultivation of said cell in suspension, with the proviso that the medium does not contain dextran sulfate.

17. (Amended) The method of claim 16, wherein said polysulfonated or polysulfated compound is selected from the group consisting of [dextran sulfate,] heparin, heparan sulfate, chondroitin sulfate, dermatan sulfate, pentosan sulfate and a proteoglycan.

22. (Twice Amended) A method of cultivating a mammalian cell in suspension *in vitro*, comprising:

(a) obtaining a mammalian cell to be cultivated in suspension; and

(b) contacting said cell with a serum-free, chemically defined cell culture medium obtained by combining a basal medium with at least one polyanionic or polycationic compound, wherein said medium supports the cultivation of said cell in suspension, with the proviso that the medium does not contain dextran sulfate.

24. (Amended) The method of claim 23, wherein said polysulfonated or polysulfated compound is selected from the group consisting of [dextran sulfate,] heparin, heparan sulfate, chondroitin sulfate, dermatan sulfate, pentosan sulfate and a proteoglycan.

106. (Thrice Amended) A method of cultivating mammalian cells in suspension culture and/or expressing a recombinant protein, said method comprising:

(a) contacting said cells with a eukaryotic cell culture medium comprising a Fe^{2+} chelate and/or a Fe^{3+} chelate, and a Zn^{2+} salt, wherein said Fe^{2+} chelate, if present, said Fe^{3+} chelate, if present, and said Zn^{2+} salt are present in an amount which supports the growth of mammalian cells in culture, said medium further comprising a polyanionic or polycationic compound, and

wherein said medium is capable of supporting the growth of mammalian cells in suspension culture and/or the expression of recombinant protein;

wherein said medium does not contain insulin or dextran sulfate; and

(b) cultivating said mammalian cells under conditions suitable to support the growth of said cells and/or the expression of said recombinant protein.

107. (Amended) The method according to claim 106, [further comprising a polyanionic or polycationic compound,] wherein said polyanionic or polycationic compound is present in an amount sufficient to prevent cell clumping and/or increase the level of recombinant protein expression.

109. (Amended) The method according to claim 108, wherein said polysulfonated or polysulfated compound is selected from the group consisting of [dextran sulfate,] heparin, heparan sulfate, chondroitin sulfate, dermatan sulfate, pentosan sulfate and a proteoglycan.

158. (Amended) A method of cultivating a mammalian cell in suspension *in vitro*, comprising:

(a) obtaining a mammalian cell to be cultivated in suspension; and

(b) contacting said cell with a serum-free, non-animal derived cell culture medium comprising at least one polyanionic or polycationic compound, wherein said medium supports the cultivation of said cell in suspension, with the proviso that the medium does not contain dextran sulfate.